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FACTORS AFFECTING THE CEREBROVASCULAR RESPONSE TO NORADRENALINE IN THE DOG

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1 Noradrenaline infused into the internal carotid artery of the dog (0.01-1 $\mu g\ kg^{-1}\ min^{-1}$) constricts the blood vessels of the cortex. This constriction is mediated by the action of noradrenaline on α-adrenoceptors of the cerebral arteries.

2 Intravenous (1 $\mu g\ kg^{-1}\ min^{-1}$) or intra common carotid arterial (0.01-1 $\mu g\ kg^{-1}\ min^{-1}$) infusions of noradrenaline cause an increase in cortical blood flow that can be dissociated from changes in blood pressure.

3 The effect of intravenous noradrenaline on the cortical blood vessels and metabolism is blocked by high $PaCO_2$ levels, or by the prior administration of (±)-propranolol. (+)-Propranolol is without such effect.

4 Following section of both vagi and both sinus nerves, intravenous noradrenaline fails to cause an increase in cortical blood flow.

5 In another series of animals the area of the carotid bifurcation was vascularly isolated and perfused with blood from a second dog. Chemoreceptor and baroreceptor activity was shown to be intact.

6 Administration of 5% CO_2 to the donor dog caused an increase in cerebral blood flow in the recipient dog.

7 Administration of intravenous noradrenaline (1.0 $\mu g\ kg^{-1}\ min^{-1}$) to the donor animal caused an increase in cerebral blood flow, cerebral O_2 and glucose utilization of the recipient.

8 Administration of 5% CO_2 and intravenous (−)-noradrenaline (1.0 $\mu g\ kg^{-1}\ min^{-1}$) caused a further increase in flow and metabolism.

9 This evidence suggests that the cerebrovasodilatation observed following intravenous noradrenaline is reflex and is triggered by chemoreceptor activity.

10 The evidence also suggests that the antagonism of the cortical dilatory effects of intravenous noradrenaline by raised $PaCO_2$ in the intact animal must be at a site different from the peripheral chemoreceptors.

Introduction

The cerebral vasculature, in contrast with that in other beds was until fairly recently considered to be almost entirely regulated by local chemical changes, e.g. PCO_2 or pH (Kety, 1960). However, it has now been suggested that cerebral blood vessels are reflexly controlled and that the carotid body chemoreceptors and carotid sinus baroreceptors initiate many of the cerebrovascular responses to hypoxia, hypercapnia and hypotension (Ponte & Purves, 1974). It appears reasonably certain that cerebral vessels are innervated in a similar fashion to those in other vascular beds. There is a great deal of morphological (Dahl & Nelson, 1964; Lavrentieva, Mchedlishvili & Plechkova, 1968; Iwayama, 1970; Iwayama, Furness & Burnstock, 1970) and histochemical (Falck, Nielsen & Owman, 1968; Ohgushi, 1968; Kajikawa, 1969) evidence to show that in most species there is an adrenergic pathway originating in the superior cervical ganglion which is a constrictor. There is also a dilator pathway, which may be cholinergic, that is carried by the VIIth cranial nerve.

Stimulation of the cervical sympathetic nerve causes unequivocal vasoconstriction (James, Millar & Purves, 1969; Harper, Deshmukh, Rowan & Jennett, 1972; D'Alecy & Feigl, 1972).

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Noradrenaline has been demonstrated in the nerve terminals (Falck *et al.*, 1968; Ohgushi, 1968) and is therefore likely to be the transmitter involved in the vasoconstrictor response. Although noradrenaline causes constriction of cerebral arterioles *in vitro* (Nielsen & Owman, 1971) its action *in vivo* is most uncertain. An increase, a decrease and no change in cerebral blood flow have all been reported in a recent review (Carpi, 1972).

Ponte & Purves (1974) have demonstrated in a series of experiments on the baboon that stimulation of vascularly isolated carotid body chemoreceptors with venous blood invariably caused a rise in regional cerebral blood flow. This response was abolished if the VIIth cranial nerves, purported to carry vasodilator nerve fibres, were cut intracranially. Cerebral blood flow varied inversely with carotid sinus pressure when cerebral perfusion pressure was held constant.

In the dog noradrenaline has been shown to cause an increase in the afferent discharge from the carotid body chemoreceptors (Black, Comroe & Jacobs, 1972). Some of the changes observed in the cerebral circulation following noradrenaline administration could, therefore, not only be due to a direct effect on the vessel wall, or secondary to blood pressure changes but could possibly be caused by activation of the carotid body chemoreceptors.

Some years ago we demonstrated that hypercapnia attenuated the vasodilator response of the cerebral circulation to an isoprenaline infusion (Xanalatos & James, 1972). It seemed appropriate therefore to determine what factors could affect the cerebrovascular response to noradrenaline in addition to the obvious ones of dose and route.

Methods

Mongrel dogs of mean weight 15 kg (s.d. ± 2) were anaesthetized with sodium pentobarbitone in a dosage of 25 mg/kg body weight. Tracheostomy was carried out and the dogs were ventilated at constant rate and depth throughout the experiment with a Starling respirator.

The right femoral vein was catheterized with a polyethylene catheter, through which maintenance doses of sodium pentobarbitone and experimental drugs were administered. A similar catheter placed in the aorta via the right femoral artery enabled blood pressure and arterial blood samples to be obtained. The arterial blood pressure was monitored with a Bell and Howell transducer in conjunction with a Devices preamplifier and subunit and the mean obtained electronically.

Cerebral blood flow

Cerebral blood flow was measured by the method of Ingvar & Lassen (1962) using the intracarotid injection of ^{85}krypton. Because 99% of the emissions from ^{85}krypton are β-particles and since the maximum penetration of these in brain tissue is only 2.5 mm (Glass, Harper & Glover, 1962) recording is almost totally from the cerebral cortex.

The left superior thyroid artery was identified and a fine polyethylene catheter introduced into the common carotid artery via this vessel. The catheter was directed towards the heart for a distance of 2 cm, so that the krypton injected through it would be washed upwards by the carotid arterial flow. It was felt that better mixing would be obtained in this way.

Craniotomy and removal of the dura was carried out as suggested by Ingvar & Lassen (1962).

Sufficient ^{85}krypton gas dissolved in about 1 ml of 0.9% w/v NaCl solution (saline) was injected slowly over approximately 1 min so that a constant plateau of radioactivity was monitored over the left parietal region for at least 45 seconds. The maximum count rate was always a factor of at least fifty times background. A ratemeter time constant of 5 s was used, and the counting scale employed was either 0.3 K or 1.0 K. Cerebral blood flow was then obtained from the analysis of the first 100 s of the ensuing decay curve as suggested by Lassen (1959). Radioactivity was measured with an end window Mullard Geiger Muller tube of effective window diameter 9 mm which was placed in such a way that large vessels were not within the counting field (Ingvar & Lassen, 1962). The Geiger Muller counter was coupled to a rate meter (Ekco Electronics Type N 522). The saturation and decay curves were recorded on a two channel potentiometric recorder (Smiths Industries Servoscribe 2, Type T/821).

A fine saggital sinus catheter was placed in such a way that flow was not impeded but samples of cortical venous blood could be obtained for blood gas analysis.

Cerebral O_2 and glucose metabolism were calculated as the product of flow and the arteriovenous difference. In this calculation it was assumed that the superior saggital sinus drains blood only from the cortex. There is good evidence in the dog to justify this assumption (Hegedus & Shackleford, 1965). Oxygen content was measured by the method of Linden, Ledsome & Norman (1965) and glucose by a glucose oxidase method (Trinder, 1969). pH, Pa_{O_2} and Pa_{CO_2} were measured with appropriate radio-

meter electrodes. The values were corrected for changes in ambient temperature according to the normogram of Severinghaus, Stupfel & Bradley (1965).

Experimental design

A period of one hour was allowed to elapse between completion of the surgery and starting the experiment. In each animal three sets of resting control measurements were made, 15 min apart, before any experimental procedure was started. The design of individual groups of experiments was as follows:

1. *Noradrenaline and CO_2 administration* (7 dogs) The effect of 5% CO_2 administration for 15 min was first assessed. Then whilst the animal was breathing room air (−)-noradrenaline was infused intravenously at a dose of 1 μg per kilogram body weight per minute. Measurements were carried out after 15 min of infusion. The drug infusion was continued and 5% CO_2 in air was simultaneously administered for a further period of 15 minutes. The CO_2 was discontinued and after another 15 min a further set of values was recorded for noradrenaline alone.

2. *Propranolol and noradrenaline* (5 dogs) In the second series of experiments (±)-propranolol at a total intravenous dose of 0.33 mg/kg body weight was infused over a 30 min period. This amount of propranolol had been found in separate experiments to abolish the increase in heart rate caused by intravenous infusion of isoprenaline at a rate of 0.4 μg kg^{-1} min^{-1} for at least a 30 min period (MacDonell, 1974). This was the dose of isoprenaline used by Xanalatos & James (1972) (see discussion section). Measurements were made after 15 and 30 min of propranolol infusion. The propranolol was discontinued and noradrenaline was administered intravenously in a dose of 1 μg kg^{-1} min^{-1}. All measurements were repeated after this drug had been infused for 15 and 30 minutes.

In two additional dogs, the noradrenaline was infused following pretreatment with 0.33 mg/kg (+)-propranolol administered over 30 minutes. In one further animal, propranolol was replaced by 3.3 mg/kg practolol given over 30 minutes.

3. *Phenoxybenzamine and noradrenaline* (5 dogs) In the third group of experiments, phenoxybenzamine in a total intravenous dose of 0.67 mg/kg was infused over a 60 min period. Previous experiments (MacDonell, 1974) showed that this dose causes a 38% attenuation of the maximum pressor response to an intravenous infusion of noradrenaline (1.0 μg kg^{-1} min^{-1}). In other studies phenoxybenzamine has been used to 'block' α-adrenoceptors in the dog in doses ranging from 1.0 mg/kg to 10.0 mg/kg (Carr, Cooper, Daggett, Lish, Nugent & Powers, 1967; Olivares, Smith & Aronow, 1967). However, under the present experimental conditions doses larger than the one employed were found to cause a precipitous fall in blood pressure.

When the effect of the total dose of phenoxybenzamine had been recorded, noradrenaline was administered intravenously, as before (1.0 μg kg^{-1} min^{-1}).

4. *Common carotid noradrenaline administration* (7 dogs) Four doses of noradrenaline were infused into seven dogs via a fine catheter placed in the common carotid artery. The doses employed were: 0.01, 0.10, 0.50 and 1.00 μg kg^{-1} min^{-1}. Measurements were made after 15 min of infusion, and 30 min were allowed to elapse between termination of the lower dose and the start of the next higher dose.

5. *Internal carotid noradrenaline administration* (5 dogs) The left internal carotid artery was catheterized via the superior thyroid artery. Noradrenaline was infused through this in doses of 0.01, 0.10 and 1.00 μg kg^{-1} min^{-1} following the same regime as in the fourth series of experiments.

In five separate animals this procedure was repeated after a total dose of 0.067 mg/kg phenoxybenzamine had been infused into the left internal carotid artery, over a period of 30 minutes. It was assumed that approximately one tenth of the cardiac output passes up one carotid artery and hence the dose of phenoxybenzamine was one tenth of that administered intravenously in the previous experiments.

6. *Intravenous noradrenaline administration following afferent denervation* (6 dogs) Both sinus nerves and both vagosympathetic trunks were sectioned in six dogs. Afferent denervation was assumed to be complete if there was no blood pressure response to occlusion of the common carotid artery. Noradrenaline was infused intravenously in a dose of 1.0 μg kg^{-1} min^{-1}.

7. *Vascular isolation of carotid bifurcation area: effect of noradrenaline* Experiments were carried out each of which involved two dogs. The carotid bifurcation regions of one dog (the recipient) were vascularly isolated and perfused with arterial blood from a second dog (the donor) (Figure 1). The carotid bifurcations were exposed bilaterally in the recipient dog. The internal carotid, the external carotid above the junction of the lingual artery

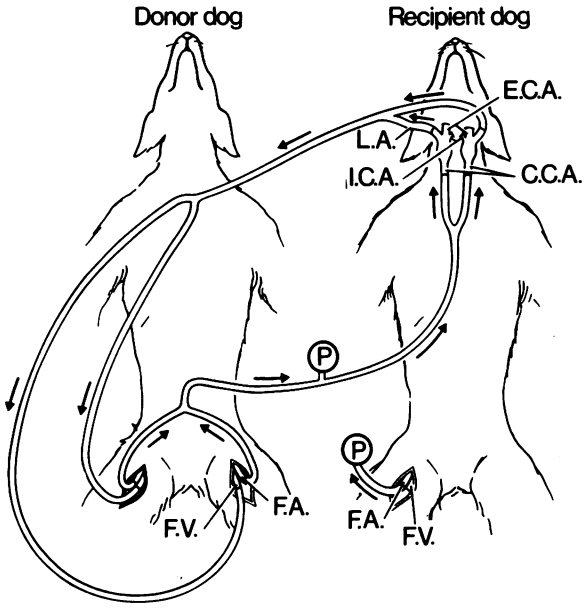

Figure 1 Final preparation involving two dogs. In the recipient dog both vagosympathetic nerve trunks had been divided. Both sinus nerves are intact. Internal carotid arteries bilaterally occluded. Brain is perfused by vertebral and many other anastomotic arteries. F.V. = femoral vein, F.A. = femoral artery, P = blood pressure transducer, I.C.A. = internal carotid artery, C.C.A. = common carotid artery, E.C.A. = external carotid artery, L.A. = lingual artery.

and all other branches such as the occipital artery of the first dog were ligated.

Blood was initially shunted from both femoral arteries into the common carotid arteries and then back into the femoral veins via catheters in the lingual arteries. Great care was taken to ensure that the sinus nerves were not damaged during this dissection. To eliminate aortic receptor responses, bilateral vagotomy was performed. The sympathetic supply to the head was also partially interrupted as this portion of the sympathetic runs with the vagus as a single trunk in the dog (Stromberg, 1964).

As soon as the remaining surgical procedure necessary for measuring cortical blood flow had been completed (see below) the donor dog was anaesthetized and tracheostomized as before. This dog was also ventilated at a constant rate and depth throughout the experiment.

Both femoral arteries and femoral veins were catheterized. Femoral arterial blood was then shunted from the donor dog into the common carotid arteries of the recipient dog. This blood was returned to the femoral veins of the donor dog via the lingual arteries of the recipient dog.

During the switching over of the blood supply to the recipient carotid bifurcation regions from recipient to donor dog, the time that this region was without a blood supply was limited to 30 seconds.

To prevent clotting of blood in the recipient carotid bifurcation areas, the donor dog was injected with 25,000 units of heparin.

The systematic arterial blood pressure of the recipient dog, and the perfusion pressure of the vascularly isolated carotid bifurcation regions were monitored with Bell and Howell pressure transducers and electronically meaned.

Cerebral blood flow was measured as before but some minor modification of the method was necessary. On this occasion the ^{85}krypton reached the parietal region via the right vertebral artery. A catheter was inserted in a retrograde manner from the superior thyroid artery on the right into the brachiocephalic artery and the gas dissolved in saline was injected as before over approximately a 1 min period so that a constant amount of radioactivity monitored over the parietal region was obtained for at least 45 seconds.

Once the preparation was complete, the following procedures were carried out: (a) At least two control measurements were recorded. (b) Five per cent CO_2 in air was administered to the donor dogs to inhale for 15 min (10 dogs).

(c) Noradrenaline in a dose of 1.0 μg kg^{-1} min^{-1} was infused intravenously into the donor dog (6 dogs). Perfusion pressure was kept constant and measurements were made at the end of a 15 min period. (d) During the continuing noradrenaline infusion, 5% CO_2 in air was simultaneously administered to the donor dog for a further 15 min period (6 dogs). Perfusion pressure was kept constant.

Drugs and chemicals

These included (−)-noradrenaline bitartrate (Koch Light Laboratories), (±)-propranolol hydrochloride and (+)-propranolol hydrochloride (ICI), phenoxybenzamine hydrochloride.

The doses used were expressed in terms of the respective salts. All drugs were dissolved in saline and were administered as above.

Results

1. *Noradrenaline and CO_2 administration*

Control values (Table 1) The mean resting value of cortical blood flow in the seven animals was 108.6 ± 9.0 (s.e. mean) ml per 100 g of cortical tissue per minute.

Mean cortical O_2 consumption was 10.9 ± 1.1 (s.e. mean) ml per 100 g per min and mean cortical glucose consumption was 16.9 ± 2.4 (s.e. mean) mg per 100 g per minute.

Mean control values of $PaCO_2$, arterial hydrogen ion concentration and mean arterial blood pressure were 38.7 ± 2.6 mmHg, 50.9 ± 2.5 nmol per litre and 144.0 ± 8.6 mmHg respectively.

These values were similar to those previously obtained from this laboratory (Xanalatos & James, 1972).

i. *Inhalation of 5% CO_2 in air* The inhalation of 5% CO_2 for a period of 15 min caused an increase in cortical blood flow in all seven dogs (Table 1). The increase in arterial CO_2 tension had no statistically significant effect upon cortical oxygen consumption, although the mean value was slightly depressed from control. Cortical glucose consumption was observed to be lower than control levels after 15 min of CO_2. The mean reduction was 6.9 mg per 100 g per minute. After the CO_2 administration had been discontinued, all the variables measured returned to previous values by the end of 15 minutes.

ii. *Intravenous infusions of noradrenaline* (Table 1) Noradrenaline was administered by con-

Table 1 Effect of 5% CO_2, noradrenaline (1 μg kg^{-1} min^{-1}) and noradrenaline plus CO_2 in the dog

	Control	*5% CO_2*	*Control*	*Noradrenaline*	*Noradrenaline +5% CO_2*	*Noradrenaline*
Cortical blood flow (ml 100 g^{-1} min^{-1})	108.6 ±9.0	147.9* ±10.2	107.1 ±9.6	138.7* ±13.5	92.6*+ ±8.0	135.3* ±8.6
Cortical O_2 consumption (ml 100 g^{-1} min^{-1})	10.9 ±1.1	9.9* ±0.8	11.3 ±1.3	15.2* ±2.0	7.2*+ ±0.6	14.7* ±0.8
Cortical glucose consumption (mg 100 g^{-1} min^{-1})	16.9 ±2.4	9.9* ±0.7	16.3 ±2.1	30.7* ±3.6	15.1+ ±4.0	31.0* ±6.0
Arterial CO_2 tension (mmHg)	38.7 ±2.6	59.9* ±3.0	38.4 ±2.5	41.9* ±2.9	62.7*+ ±3.1	43.7 ±3.1
Arterial hydrogen ion concentration (nmol/litre)	50.9 ±2.5	65.5* ±2.3	52.2 ±2.5	55.4* ±2.7	74.2*+ ±2.3	58.5* ±3.0
Mean arterial blood pressure (mmHg)	144.0 ±8.6	149.7* ±7.1	145.0 ±7.5	149.3 ±7.4	145.4 ±6.8	145.4 ±4.7

All measurements made at the end of a 15 min period. All PaO_2 measurements were above 100 mmHg. Means ± s.e. mean are shown. $n = 7$.

* Significantly different from 1st control by paired analysis at 5% level.

\+ Significantly different from preceding noradrenaline levels by paired analysis at 5% level.

tinuous intravenous infusion in a dose of 1.0 μg/kg body weight per minute. In all experiments, at the end of 15 min of noradrenaline infusion cortical blood flow was higher than resting control values. Both cortical O_2 and cortical glucose consumption were increased, although the elevation in O_2 consumption was not as great as that in glucose consumption. Blood pressure, which was initially elevated by the noradrenaline infusion, had returned to within control levels after 15 min of infusion and was thus at this time not significantly different from control values (Table 1).

iii. *Noradrenaline and simultaneous 5% CO_2* (Table 1) Five per cent CO_2 in air was then readministered during the continuing noradrenaline infusion for a period of 15 minutes. Combined noradrenaline and CO_2 caused a fall in cortical blood flow to a mean value of 93 ml per 100 g per minute, which was lower than not only the initial noradrenaline level but also the initial control values.

Cortical O_2 and glucose consumptions both fell from their previously elevated levels. Oxygen utilisation was also lower than the control levels, but glucose uptake fell only to resting values.

The fall in blood flow occurring at a time when arterial blood pressure was constant suggests that cortical vasoconstriction was taking place.

The administration of CO_2 was then terminated, but the infusion of noradrenaline continued. After 15 min, all the variables measured returned to those values observed when noradrenaline had previously been administered alone. This suggested that the changes occurring with noradrenaline plus CO_2 were not due to the increasing cumulative dose of noradrenaline, but due to the addition of CO_2.

2. *Propranolol and noradrenaline* (Table 2)

a. *Effect of propranolol* At the end of the propranolol infusion, cortical blood flow, cortical O_2 and glucose consumption and mean arterial blood pressure were all significantly lower than control values.

b. *Effect of noradrenaline after propranolol* (Table 2) As soon as the final propranolol measurements had been made, noradrenaline in the same dose as in the previous experiments (1.0 μg kg^{-1} min^{-1}) was infused intravenously. After 15 min of infusion, a further fall in both cortical blood flow and O_2 uptake was seen (Figure 2). Cortical glucose consumption was more variable, but tended to remain low.

The fall in mean arterial blood pressure due to propranolol was reversed by noradrenaline. The

Table 2 Effect of propranolol (total dose 0.33 mg/kg given i.v. over 30 min) and noradrenaline (1.0 μg kg^{-1} min^{-1}, i.v.) immediately following propranolol in dog.

	Control	*Control*	*Propranolol*	*Propranolol*	*Noradrenaline*	*Noradrenaline*
Cortical blood flow (ml 100 g^{-1} min^{-1})	98.6 ±7.2	99.8 ±7.3	74.4* ±10.8	76.6* ±6.8	56.8* ±4.3	77.0* ±7.3
Cortical O_2 consumption (ml 100 g^{-1} min^{-1})	10.6 ±0.9	10.7 ±1.1	8.3* ±1.2	9.3* ±0.9	7.0* ±0.7	10.7 ±1.1
Cortical glucose consumption (mg 100 g^{-1} min^{-1})	15.4 ±1.3	15.7 ±1.4	12.9 ±2.3	11.0* ±0.7	11.6* ±1.6	14.1* ±1.3
Mean arterial blood pressure (mmHg)	127.0 ±13.2	125.6 ±14.9	117.6* ±13.4	108.2* ±11.4	126.4 ±12.2	123.4 ±12.2
Arterial hydrogen ion concentration (nmol/litre)	46.8 ±2.6	46.1 ±2.3	44.4 ±2.8	44.2 ±2.2	46.2 ±3.1	48.4 ±4.1
$PaCO_2$ (mmHg)	32.6 ±2.9	32.2 ±2.9	30.4 ±3.7	30.4 ±3.6	30.8 ±3.4	31.2 ±3.3

All measurements made at the end of 15 min periods. All PaO_2 measurements above 100 mmHg. Means ± s.e. mean are shown. $n = 5$.
* Significantly different from 1st control values by paired analysis at the 5% level.

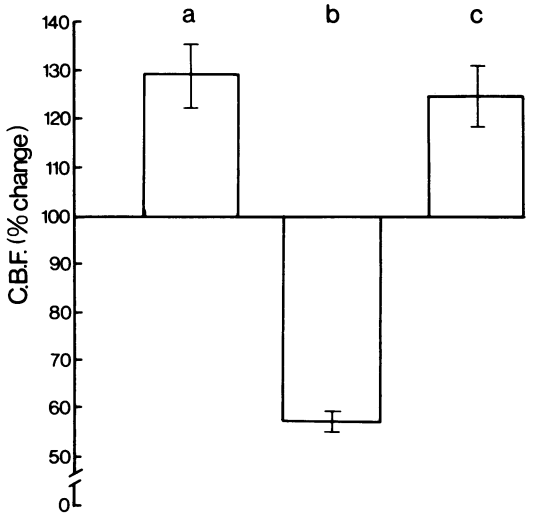

Figure 2 Changes in cortical blood flow in response to 15 minutes of intravenous infusion of noradrenaline (1.0 μg kg^{-1} min^{-1}) in dog. (a) After no pretreatment (n = 7), (b) after pretreatment with propranolol (0.33 mg/kg) (n = 5), (c) after pretreatment with phenoxybenzamine (0.67 mg/kg) (n = 5). Cerebral cortical blood flow (C.B.F.) expressed as percentage of control (= 100%). Vertical bars show s.e. mean.

fall in blood flow occurring at a time when arterial blood pressure increased suggests that cortical vasoconstriction was taking place.

After 30 min of noradrenaline infusion cortical flow, O_2 and glucose consumption were seen to increase back towards control levels. Both flow and glucose utilization were still somewhat depressed, but O_2 consumption was no longer significantly different from control.

c. *Effect of noradrenaline after (+)-propranolol* In an attempt to establish whether the observed effect of propranolol on the response by cortical blood flow and metabolism to noradrenaline was due to its β-adrenoceptor blocking properties or to its membrane stabilizing activity, two further experiments were carried out. In these, noradrenaline was administered intravenously in the same dose as before following pretreatment with (+)-propranolol. This drug, which has little β-adrenoceptor blockading activity, but has similar local anaesthetic properties to those of (±)-propranolol (Howe & Shanks, 1966) was given in an intravenous dose of 0.33 mg/kg over a 30 min period. Pretreatment with this drug failed to cause any changes in flow or metabolism or markedly alter the response to the intravenous administration of noradrenaline.

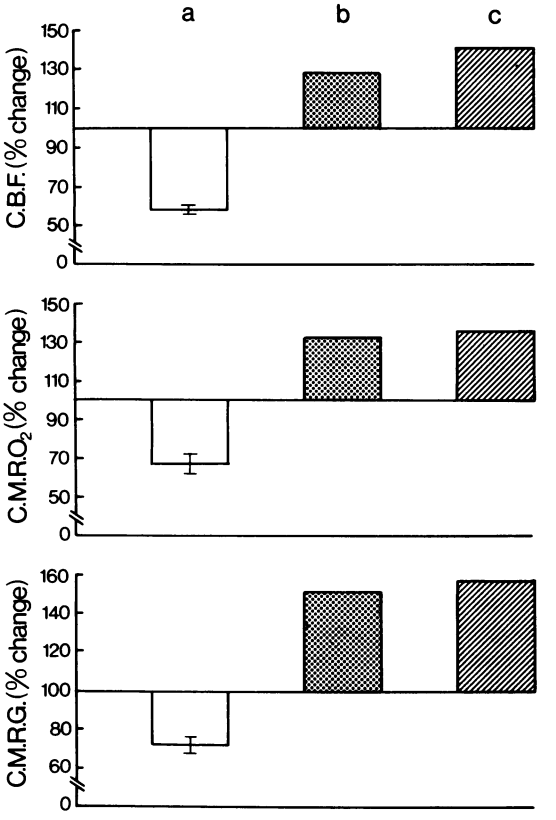

Figure 3 Effect of noradrenaline (1.0 μg kg^{-1} min^{-1}, 15 min intravenous infusion) on cortical blood flow, cortical O_2 consumption and cortical glucose consumption expressed as a percentage change from control (= 100%). (a) After pretreatment with (±)-propranolol (0.33 mg/kg) (n = 5), (b) after pretreatment with (+)-propranolol (0.33 mg/kg, average of 2 experiments), (c) after pretreatment with practolol (3.3 mg/kg), 1 experiment. C.B.F. = cortical blood flow, C.M.R.O_2 = cortical O_2 consumption, C.M.R.G. = cortical glucose consumption. Vertical bars show s.e. mean.

The changes observed after 15 min of intravenous noradrenaline following prior administration of (+)-propranolol are represented in Figure 3.

These results, although from only two experiments, suggest that membrane stabilization was not responsible for the altered cerebrovascular response to intravenous noradrenaline following treatment with (±)-propranolol.

d. *Effect of noradrenaline after practolol* Another experiment was carried out, this time practolol was given before noradrenaline. Practolol, besides being a selective blocker of

β_1-adrenoceptors (Dunlop & Shanks, 1968) does not enter the brain to any great extent (Estler & Ammon, 1969). Because propranolol readily passes the blood brain barrier (Laverty & Taylor, 1968) it was thought possible that the observed action of this drug could be centrally mediated.

In clinical practice, propranolol has been used in a dose approximately one tenth of that used with practolol (Meier, 1972). Hence, in the present study, 3.3 mg/kg practolol (ten times the dose of (±)-propranolol used) was administered intravenously over a 30 min period. Pretreatment with practolol, like (+)-propranolol, failed to alter markedly the cerebrovascular response to an intravenous infusion of noradrenaline (Figure 3).

3. *Phenoxybenzamine and noradrenaline* (Table 3)

a. *Effect of phenoxybenzamine (0.67 mg/kg)* This intravenous dose of phenoxybenzamine caused a substantial drop in mean arterial blood pressure. For this reason the drug was given slowly over a period of 1 h in an attempt to block cerebrovascular α-adrenoceptors without causing a precipitous fall in blood pressure.

The fall in blood pressure was usually accompanied by a small decrease in cortical blood flow. There was no consistent change in mean cortical O_2 or glucose consumption. In one of the five animals, phenoxybenzamine caused a decrease in cortical O_2 consumption whereas in the remaining four an increase occurred. Similarly, in another dog, phenoxybenzamine caused a substantial fall in cortical glucose consumption, whereas in the remaining four this variable increased.

b. *Noradrenaline following phenoxybenzamine* (Table 3) After intravenous infusion of noradrenaline in the usual dose of 1.0 μg per kg per min for 15 min, both cortical blood flow and cortical O_2 consumption were significantly elevated above control values (Figure 2).

Changes in cortical glucose consumption were, however, more variable. In three animals this was higher than controls at this time, but in two, glucose utilization fell.

Mean arterial blood pressures increased back towards control values, but this change was less than that in flow, suggesting that noradrenaline after phenoxybenzamine caused cortical vasodilation.

The values for cortical blood flow and metabolism increased again slightly during the continuing infusion of noradrenaline for another 15 min period, and these values were then all statistically different from control levels.

Mean arterial blood pressure failed to show any further consistent change.

4. *Common carotid noradrenaline administration*

Cortical O_2 and glucose consumption were not measured because the noradrenaline was infused unilaterally. Venous samples for metabolism recordings have to be taken from the superior saggital sinus, which drains both sides of the cerebral cortex, meaning that metabolism measurements following unilateral administration of a drug would not be representative of metabolic changes in the area of cortex over which flow was measured.

Thus, in this group of experiments, as in the next series, flow was measured on the same side as

Table 3 Effect of phenoxybenzamine (total dose 0.67 mg/kg infused i.v. over one hour) and noradrenaline (1.0 μg kg^{-1} min^{-1}, i.v.) following phenoxybenzamine in the dog

	Control	*Control*	*Phenoxybenzamine*	*Noradrenaline*	*Noradrenaline*
Cortical blood flow ($ml\ 100\ g^{-1}\ min^{-1}$)	88.2 ±7.5	88.4 ±8.2	77.4* ±8.1	109.8* ±9.9	114.8* ±8.8
Cortical O_2 consumption ($ml\ 100\ g^{-1}\ min^{-1}$)	8.8 ±0.8	8.8 ±0.9	9.6 ±1.2	13.1* ±1.8	15.2* ±1.9
Cortical glucose consumption ($mg\ 100\ g^{-1}\ min^{-1}$)	13.2 ±2.0	13.0 ±1.4	13.6 ±2.0	19.6 ±3.5	23.2* ±2.2
Mean arterial blood pressure (mmHg)	132.8 ±8.5	132.8 ±8.1	105.0* ±5.7	111.0* ±5.2	112.2* ±5.9
Arterial PCO_2 (mmHg)	37.4 ±1.9	36.6 ±2.4	36.0 ±2.4	38.6 ±3.3	38.8 ±3.1

All measurements (except those at the end of the phenoxybenzamine infusion) were made at the end of 15 min periods. All PaO_2 measurements above 100 mmHg. Means ± s.e. mean are shown. $n = 5$.
* Significantly different from 1st control values by paired analysis at the 5% level.

the infusions of noradrenaline. The results are shown in Table 4.

a. *Infusions of 0.01 μg kg^{-1} min^{-1}* Noradrenaline infused into the common carotid artery at this dose for 15 min, caused no significant change in cortical blood flow or systemic arterial blood pressure. In three of the seven experiments, however, cortical blood flow fell, but in only two by large amounts.

b. *Infusions of 0.1 μg kg^{-1} min^{-1}* No consistent change followed these doses of noradrenaline. On two occasions cortical blood flow increased, but in the remaining five experiments there was a tendency for flow to fall. No significant change in mean arterial blood pressure occurred.

c. *Infusions of 0.5 μg kg^{-1} min^{-1}* At the end of the 15 min infusion of noradrenaline at this dose, there was a significant increase in cortical blood flow. Mean arterial blood pressure did not significantly change.

d. *Infusions of 1.0 μg kg^{-1} min^{-1}* At this highest dose used, cortical blood flow was again significantly raised above control values. The mean value was, however, somewhat lower than with the previous dose of 0.5 μg kg^{-1} min^{-1}.

All values returned to within resting levels during the 30 min control periods between each dose.

5. *Internal carotid noradrenaline administration* (Table 5)

i. *Infusion of 0.01 μg kg^{-1} min^{-1}* This dose of noradrenaline into the internal carotid artery caused a small decrease in cortical blood flow and no significant change in mean arterial blood pressure (Figure 4).

ii. *Infusion of 0.1 μg kg^{-1} min^{-1}* A decrease in cortical blood flow occurred at the end of 15 min of this dose of noradrenaline infused into the internal carotid artery. This fall in flow was greater than observed with the previous dose. Mean arterial blood pressure was not significantly changed from control levels (Figure 4).

iii. *Infusions of 1.0 μg kg^{-1} min^{-1}* These relatively large doses of noradrenaline directly into the internal carotid artery caused a similar reduction in cortical blood flow to that seen with

Table 4 Effect of infusions of noradrenaline into the left common carotid artery of the dog.

	Common carotid noradrenaline infusions (μg kg^{-1} min^{-1})				
	Control	*0.01*	*0.10*	*0.50*	*1.00*
Cortical blood flow (ml 100 g^{-1} min^{-1})	88.1 ±12.1	82.3 ±12.8	79.0 ±14.6	120.4* ±16.5	108.7* ±16.0
Mean arterial blood pressure (mmHg)	133.4 ±6.5	134.4 ±6.8	133.4 ±6.1	134.4 ±5.8	133.3 ±6.6

Each dose was infused for 15 min at the end of which the measurements were made. A 30 min control period (not shown) was allowed to elapse between the different doses. All PaO_2 measurements above 100 mmHg. Means ± s.e. mean are shown. $n = 7$ (for each dose).
* Significantly different from 1st control by paired analysis at 5% level.

Table 5 Effect of noradrenaline infused for 15 min into the left internal carotid artery of the dog

	Internal carotid noradrenaline infusions (μg kg^{-1} min^{-1})				
	Control	*0.01*	*0.10*	*1.00*	*Control*
Cortical blood flow (ml 100 g^{-1} min^{-1})	74.2 ±8.6	64.4* ±7.1	50.0* ±6.3	50.4* ±7.2	76.0 ±8.0
Mean arterial blood pressure (mmHg)	138.4 ±5.1	130.5 ±4.3	136.6 ±5.4	151.0 ±9.4	137.6 ±3.6

All PaO_2 measurements above 100 mmHg. Means ± s.e. mean are shown. $n = 5$.
* Significantly different from 1st control by paired analysis at 5% level.

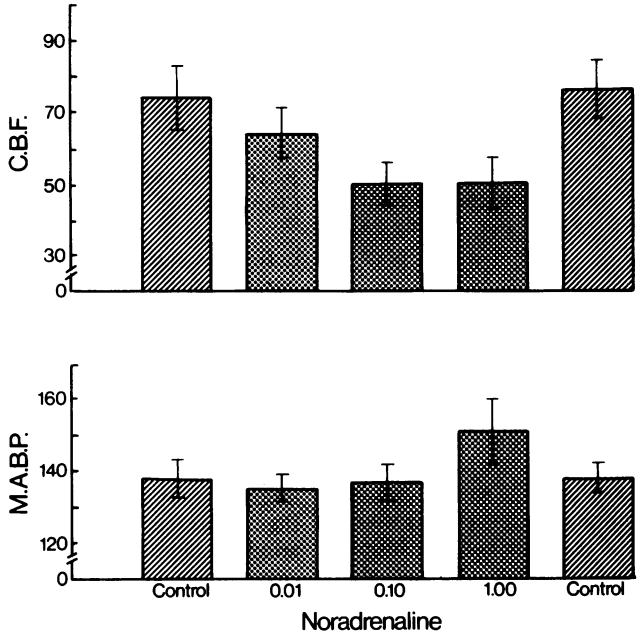

Figure 4 Effect on cortical blood flow and mean arterial blood pressure of increasing doses of noradrenaline infused for 15 min into the left internal carotid artery of the dog. Doses given in $\mu g\ kg^{-1}\ min^{-1}$. C.B.F. = cortical blood flow (ml $100\ g^{-1}\ min^{-1}$). M.A.B.P. = mean arterial blood pressure (mmHg). Vertical bars show s.e. mean, $n = 5$.

the previous dose of 0.1 $\mu g\ kg^{-1}\ min^{-1}$. There was a tendency for mean arterial blood pressure to increase.

All values returned to within control levels during the 30 min control period following termination of each infusion of each dose used.

Internal carotid noradrenaline infusions after pretreatment with phenoxybenzamine The internal carotid arterial infusions of noradrenaline were repeated in another five dogs after phenoxybenzamine 0.067 mg/kg had been infused during 30 min (Table 6).

After control measurements, cortical blood flow was recorded at the end of the phenoxybenzamine infusion, and after 15 min of noradrenaline infusions (0.01, 0.10 and 1.00 $\mu g\ kg^{-1}\ min^{-1}$). As before, a 30 min control period was allowed between the different noradrenaline doses. During this time, all the variables measured returned to within their internal resting values.

As can be seen from Figure 5, phenoxy-

Table 6 Effect of phenoxybenzamine (0.067 mg/kg) infused into the left internal carotid artery, and of 15 min infusions of noradrenaline into the left internal carotid artery after phenoxybenzamine in the dog

				Internal carotid noradrenaline ($\mu g\ kg^{-1}\ min^{-1}$)		
	Control	*Control*	*Phenoxybenzamine*	*0.01*	*0.10*	*1.00*
Cortical blood flow ($ml\ 100\ g^{-1}\ min^{-1}$)	85.2 ±7.6	85.8 ±8.2	90.2* ±7.7	90.6 ±7.6	87.0 ±7.3	89.0 ±7.2
Mean arterial blood pressure (mmHg)	131.8 ±10.1	132.6 ±9.9	129.8 ±11.5	131.4 ±11.9	130.8 ±12.7	132.8 ±12.9

All PaO_2 measurements above 100 mmHg. Means ± s.e. mean are shown. $n = 5$.
* Significantly different from 1st control by paired analysis at 5% level.

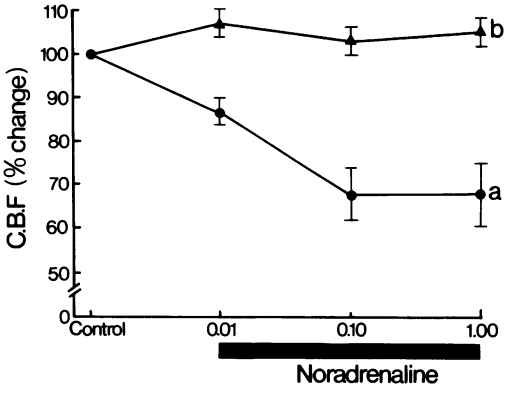

Figure 5 Changes in cortical blood flow during 15 min infusions of increasing doses of noradrenaline (0.01, 0.10 and 1.00 μg kg^{-1} min^{-1} into the left internal carotid artery. (a) Following no pretreatment (●) $n = 5$, (b) following pretreatment with phenoxybenzamine (1.0 mg infused into the internal carotid artery over a period of 30 min) (▲) $n = 5$. C.B.F. = cortical blood flow expressed as percentage changes from control (= 100%). Vertical bars show s.e. mean.

benzamine completely abolished the previously observed cortical vasoconstrictor action of all the doses of noradrenaline given directly into the internal carotid artery. These results suggest that if noradrenaline is administered directly into the internal carotid artery, an α-adrenoceptor mediated vasoconstriction occurs in the cerebral cortex.

6. *Intravenous noradrenaline following afferent denervation*

Noradrenaline infused intravenously at a dose of 1.0 μg kg^{-1} min^{-1} for 30 min caused no significant change in cortical blood flow. It should be noted however, that the initial flow values were low.

It was noticed that in these preparations, the blood pressure response to noradrenaline became attenuated more slowly than previously observed. Thus in some experiments blood pressure was still elevated well above control values even after 30 min of noradrenaline infusion.

7. *Effect of noradrenaline in cross perfusion experiments*

Baroreceptor and chemoreceptor reflexes To ensure that the sinus nerves had not been damaged during the preparation, the following tests were carried out:

The perfusion pressure in the system supplying the vascularly isolated carotid bifurcation area of the recipient dogs was raised and then lowered. This was done by partially occluding the outflow and inflow catheters to the system respectively, by means of a screw clip. The change, in the opposite direction, of the recipient systemic arterial blood pressure was taken to indicate that the carotid baroreceptors were functioning normally (Heymans & Neil, 1958).

The recipient dogs were allowed to ventilate spontaneously for a time and resting respiratory rate was monitored; 5% CO_2 was then administered to the donor dog. The resulting increase in respiratory rate and decrease in arterial PCO_2 of the recipient animal was assumed to demonstrate that this dog's carotid body chemoreceptors were also functioning normally (Biscoe, Purves & Sampson, 1970).

a. *Control values* At least two control values were recorded before each experimental procedure. The mean control cortical blood flow was 66.1 (s.e. mean ± 5.0) ml 100 g^{-1} min^{-1}. Cortical O_2 consumption was (s.e. mean ± 0.8) ml 100 g^{-1} min^{-1}, and cortical glucose consumption was 11.3 (s.e. mean ± 1.3) mg 100 g^{-1} min^{-1}.

During most procedures there was no significant change in A-V O_2 or glucose differences, hence changes in cortical metabolism were qualitatively similar to those in flow.

Table 7 The effect of noradrenaline (1.0 μg kg^{-1} min^{-1}) for 15 and 30 min following bilateral vagus and sinus nerve section in the dog

	Control	*Control*	*Noradrenaline*	*Noradrenaline*	*Control*
Cortical blood flow (ml 100 g^{-1} min^{-1})	55.8 ±11.8	59.0 ±13.8	69.7 ±12.3	67.5 ±13.3	52.8 ±11.0
Mean arterial blood pressure (mmHg)	127 ±6.5	129 ±5.8	165* ±6.1	147 ±10.1	117 ±16.5

All PaO_2 measurements above 100 mmHg. $n = 6$.
* Significantly different from 1st control by paired analysis at 5% level.

Table 8 Cross perfusion experiments. Effect on recipient dog of: (a) two consecutive control periods, (b) administration of 5% CO_2 to donor dog, (c) noradrenaline (1 μg kg^{-1} min^{-1}, i.v.) administered to donor dog for 15 min, (d) noradrenaline (1 μg kg^{-1} min^{-1}, i.v.) plus 5% CO_2 administered to donor dog for 15 minutes

	C.B.F.		*M.A.B.P.*		*P.P.*		$PaCO_2$		*C.M.R.O*$_2$		*C.M.R.G.*	
	C	*C*	*C*	*C*	*C*	*C*	*C*	*C*	*C*	*C*	*C*	*C*
a. Control	66.1 ±5.0	64.3 ±5.6	124 ±10.2	122 ±11.2	96 ±9.6	94 ±10.0	38.1 ±2.7	38.7 ±3.2	9.0 ±0.8	8.7 ±0.7	11.3 ±1.3	11.0 ±1.2
	C	*Exp*	*C*	*Exp*	*C*	*Exp*	*C*	*Exp*	*C*	*Exp*	*C*	*Exp*
b. 5% CO_2 to donor dog	67.9 ±5.0	91.7* ±7.9	123.5 ±10.2	122.0 ±10.1	95.8 ±9.6	94.0 ±7.8	42.4 ±3.3	40.3 ±3.2	9.0 ±0.8	13.3* ±1.3	11.3 ±1.3	17.1* ±2.2
c. Noradrenaline	55.3 ±2.7	83.0* ±5.1	105.7 ±17.0	111.2 ±19.5	101.8 ±9.3	108.5 ±11.8	37.2 ±4.2	38.0 ±4.4	7.9 ±0.7	11.6* ±1.8	9.5 ±1.6	16.3* ±1.7
d. Noradrenaline + 5% CO_2	75.8 ±5.8	89.3* ±5.0	104.3 ±13.3	109.8 ±15.4	106.7 ±12.5	110.7 ±10.6	38.0 ±3.7	37.7 ±4.3	10.8 ±1.5	12.9* ±1.7	14.7 ±1.9	17.2 ±2.3

For procedures b, c and d, experimental values are compared with immediately preceding control values. Means ± s.e. mean are shown. n = 10 for (a) and (b); n = 6 for (c) and (d).

* Significantly different from preceding control by paired analysis ($P < 0.05$).

C = control, Exp = experimental, C.B.F. = Cortical blood flow (ml 100 g^{-1} min^{-1}), C.M.R.O_2 = Cortical O_2 consumption (ml 100 g^{-1} min^{-1}), M.A.B.P. = mean arterial blood pressure of recipeint dog (mmHg), P.P. = perfusion pressure to recipient carotid bifurcation areas (mmHg), $PaCO_2$ = arterial CO_2 tension in recipient dog (mmHg). All measurements of PaO_2 in recipient and donor dogs above 100 mmHg.

b. *CO_2 (5%) to donor dog* After 15 min of CO_2 administration to the donor dog, recipient cortical blood flow, O_2 and glucose consumption were significantly elevated above control values.

There was no significant change in recipient systemic arterial blood pressure.

c. *Noradrenaline to donor dog* The intravenous infusion of noradrenaline to the donor dog consistently caused an increase in cortical blood flow and metabolism in all of the six experiments. There was no significant change in recipient systemic arterial blood pressure after 15 minutes. Perfusion pressure was kept constant despite an initial rise in the blood pressure of the donor dog.

d. *Noradrenaline plus CO_2 to donor dog* A further increase in cortical blood flow and O_2 consumption above the already elevated noradrenaline levels was seen in these experiments. A further, small increase in cortical glucose consumption was also observed.

There was no change in recipient $PaCO_2$. Systemic arterial blood pressure of the recipient dog was not markedly altered, since carotid perfusion pressure was kept constant.

Discussion

The average error in the measurement of cerebral blood flow by this method has previously been shown by us to be in the region of 5% (s.d. ± 3.1%) (MacDonell, 1974). The variation in the control flows between various groups of animals studied cannot be ascribed therefore to this. Differences in age of the animals and source of supply are probably more important factors.

Inhalation of 5% CO_2 gave rise to an increase in cerebral blood flow, a small decrease in O_2 consumption and a larger decrease in cerebral glucose consumption.

The changes in cerebral blood flow, O_2 and glucose consumption during noradrenaline infusion at normal and raised CO_2 levels are very similar to those reported by us as occurring with the β-agonist, isoprenaline (Xanalatos & James, 1972). The increase in flow is unlikely to be due to an increase in blood pressure. The blood pressure rise was very largely attenuated following fifteen minutes of noradrenaline infusion.

Both isoprenaline 0.4 μg kg^{-1} min^{-1} and noradrenaline 1.0 μg kg^{-1} min^{-1} caused similar increases in O_2 consumption. However, there was not such a large rise in flow with noradrenaline as isoprenaline. When CO_2 was administered during the isoprenaline infusion, cerebral blood flow fell to control levels, whereas when given during the

noradrenaline infusion, cerebral blood flow fell to values significantly below control.

Since it has been shown that many β-adrenergic effects are abolished or attenuated by administration of CO_2 (Schroeder, Robinson, Miller & Harrison, 1970; Xanalatos & James, 1972) and also that some of the effects of noradrenaline (such as those on the heart) are β-effects (Benfey & Varma, 1964; Brick, Hutchinson & Roddie, 1966a,b) it was decided that the effect of noradrenaline infusion following the prior administration of the β-adrenoceptor blocking agent, propranolol, should be evaluated.

The blood pressure fell by 15% during the propranolol infusion, but had returned to control levels by the time the noradrenaline was administered.

The propranolol caused a slight fall in cerebral blood flow and O_2 consumption and a greater fall in glucose consumption. When noradrenaline was given intravenously a clear fall in cerebral blood flow was observed. This was accompanied by a further small fall in cerebral O_2 consumption, but glucose consumption remained at the same level.

Under these circumstances it appeared, therefore, that once the vasodilator effects of noradrenaline were attenuated, cerebral vasoconstriction ocurred.

(+)-Propranolol did not have any significant effect on its own or on the noradrenaline response. It is therefore likely that response to (±)-propranolol was due to its adrenoceptor blocking properties rather than its membrane stabilizing ones.

The administration of practolol in appropriate doses also failed to alter the response. Whether this was due to the fact that practolol is a water soluble drug and penetrates the blood brain barrier poorly or principally has only β_1-adrenoceptor blocking properties is unclear.

The effect of phenoxybenzamine on brain metabolism was variable but usually caused a small decrease in cortical blood flow and a substantial drop in mean arterial pressure. Noradrenaline administration following phenoxybenzamine resulted in the usual increase in flow and metabolism.

The observed increases in cortical blood flow during infusions of noradrenaline into the common carotid artery were similar to those obtained with intravenous noradrenaline. This suggests that the mechanisms involved in the cortical vasodilator response to the two different routes of administration were similar. Noradrenaline administered directly into the internal carotid artery, however, caused a reverse effect, and cortical vasoconstriction occurred. The failure to observe this effect following pretreatment with phenoxybenzamine suggests that the vasoconstriction was α-adrenoceptor mediated, and is in agreement with the results of Oberdoster, Lang & Zimmer (1973).

The entirely different effects of noradrenaline given into the internal and common carotid arteries in the present study suggests that the carotid sinus baroreceptors and carotid body chemoreceptors may be involved in the cerebrovascular response to the drug. Hence, noradrenaline given into the common carotid artery reaches the carotid receptors, whereas that given directly into the internal carotid artery does not. Ponte & Purves (1974) have shown that stimulation of carotid body chemoreceptors with hypercapnia or hypoxia can reflexly affect cerebral blood flow. Joels & White (1968) showed that locally applied noradrenaline can increase carotid body chemoreceptor discharge in the cat. Black *et al.*, (1972) have obatined results in the dog which indicate that noradrenaline may stimulate respiration by an action on the carotid body.

It appears, therefore, that the direct action of noradrenaline on cerebral blood vessels is α-adrenoceptor mediated vasoconstriction. However, noradrenaline administered below the level of the carotid reflexogenic areas causes cerebral vasodilatation.

Administration of noradrenaline intravenously once both vagi and sinus nerves had been cut failed to cause the usual flow increase. Cortical blood flow was initially low and it is therefore difficult to interpret these findings as conclusive evidence of the importance of the afferent nerves in the noradrenaline response. It could be argued for example that the cerebral arteries were in spasm and were incapable of dilating in the normal fashion.

In the cross perfusion experiments the resting values for cerebral blood flow were again low. Under these circumstances there was the added factor of internal carotid artery occlusion. However, the dog has very extensive intra- and extracranial communicating vessels and can in fact easily survive ligation of both common carotid arteries and both vertebral arteries (Hill, 1896; Evans & Samaan, 1936).

The control cerebral blood flow values in the deafferentation and in the cross perfusion experiments were similar. In the cross perfusion experiments when 5% CO_2 in air was administered to the donor dog the cerebral blood flow of the recipient dog increased. These results are in agreement with those of Ponte & Purves (1974). The increase in blood flow occurring at a time when mean arterial blood was relatively constant certainly argues that these vessels were able to

dilate. Furthermore, this increase is likely to be due to increased activity in the sinus nerve since section of the sinus nerve at the end of the experiment abolished the increase (3 dogs). The increase in flow that occurred following noradrenaline administration to the donor dog was also likely to be affected by this mechanism.

It has been shown that noradrenaline in the dog causes an increase in chemoreceptor discharge (Joels & White, 1968; Black *et al.*, 1972). When CO_2 and noradrenaline were given simultaneously to the donor dog a greater vasodilation in the recipient cerebral circulation occurred. The effects of both these stimuli together seemed to be additive.

Certainly this increase contrasts with the marked fall in flow found when CO_2 and noradrenaline were given together in the single dog experiments.

These results suggest that intravenous noradrenaline probably causes cerebral vasodilatation by stimulating the peripheral chemoreceptors and that the antagonist effect of 5% CO_2 administration must occur in the intact animal at a site different from the peripheral chemoreceptors.

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